Trial Statistical Analysis Plan

c02189546-02

BI Trial No.:	1315.7
Title:	A Phase I/II, Multicenter, Open-label, Dose Escalation and Randomized Trial of BI 836858 in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes Including Protocol Amendments 1, 2 3 and 4 **[c02304070-06]**
Investigational Product(s):	BI 836858
Responsible trial statistician(s):	 Phone: Fax:
Date of statistical analysis plan:	07 JAN 2020 SIGNED
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse events of special interest
ALQ	Above limit of quantification
ALT	Alanine Amino Transferase
AML	Acute Myelogenous Leukemia
AST	Aspartate Amino Transferase
ATC classification	Anatomical, Therapeutic, Chemical classification
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BLRM	Bayesian logistic regression model
BMI	Body Mass Index
BSA	Body Surface Area
CR	Complete Response
CT	Concomitant therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Data base lock
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
eCRF	Electronic case report form
EFS	Event free survival
HI	Hematologic improvement
HI-E	Hematologic improvement erythroid
HI-N	Hematologic improvement neutrophils
HI-P	Hematologic improvement platelets
ICH	International Conference on Harmonisation

Term	Definition / description
iPD	Important Protocol Deviation
IRR	Infusion related reaction
LLOQ	Lower limit of quantification
mCR	Marrow Complete Response
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
MQRM	Medical and Quality Review Meeting
MTD	Maximum tolerated dose
OR	Objective response
PD	Progressive disease
PR	Partial response
PT	Preferred term
RBC TI	Red Blood Cell Transfusion Independence
REP	Residual effect period
RP2D	Recommended phase 2 dose
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System organ class
SS	Screened set
TLS	Tumor Lysis Syndrome
TS	Treated set
ULN	Upper Limit of Normal
ULOQ	Upper limit of quantification
WHO DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per International Conference on Harmonisation E9 (ICH E9) (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization. This TSAP follows the Boehringer Ingelheim (BI) internal reference (2).

This TSAP is based on the Project Statistical Analysis Plan wherever possible. Wordings like "randomization (first administration of study treatment in non-randomized trials)" should therefore be interpreted as applicable.

SAS version 9.4 (or later) will be used for all other analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

4.1 CLARIFICATIONS

As stated in the CTP, one of the Phase I primary endpoints is "occurrence of dose limiting toxicity (DLT)". To clarify, this is defined as the number of patients with DLTs during the maximum tolerated dose (MTD) evaluation period.

4.2 CHANGES

This study was terminated prematurely during the Phase I expansion cohort stage. No patients were recruited for the Phase II part of the study. Therefore none of the Phase II analyses stated in the CTP will be performed. The rest of this TSAP specifies analyses pertaining to Phase I part of the study only.

5. ENDPOINTS

This study is an open label Phase I/II trial of BI 836858 in patients with low or intermediate-1 risk myelodysplastic syndromes. Only the Phase I part is conducted; the study is terminated with recruitment discontinued before the commencement of the Phase II part.

Phase I consists of a single arm, dose escalation stage followed by an expansion cohort stage. Dose-escalation is guided by a Bayesian logistic regression model with overdose control. The primary objectives are determination of the MTD and the recommended phase II dose (RP2D). After determination of the MTD/RP2D, two expansion cohorts—untreated or pre-treated with HMA and/or lenalidomide—are enrolled at the selected dose.

5.1 PRIMARY ENDPOINTS

The primary endpoints in the Phase I part of the trial are the MTD and the number of patients with dose limiting toxicities (DLTs) during the MTD evaluation period.

Maximum tolerated dose (MTD) and number of patients with DLTs during the MTD evaluation period:

The MTD is defined as the highest dose of BI 836858 with less than 25% risk of the true DLT rate being above 33% during the MTD evaluation period. The other primary endpoint, the number of patients with DLTs during the MTD evaluation period will be used to determine the MTD.

MTD evaluation period:

The MTD evaluation period is defined as the time from the first administration of trial medication to start of the third administration of BI 836858, excluding the day of the third administration of BI 836858. In case the third infusion of BI 836858 is not administered, the evaluation period ends 30 days after the last administration.

In case a patient has not completed the required number of administrations due to BI 836858 related toxicity, he/she will not be replaced and this will be considered as DLT. However, patients who have not completed the required number of administrations of BI 836858 for reasons other than BI 836858 related toxicity will be replaced. Patients who were replaced during the MTD evaluation period will not be considered for MTD evaluation. That is, a patient will be considered evaluable for MTD assessment if he/she received at least 2 administrations of BI 836858 or if he/she received less than 2 administrations due to DLT.

The MTD estimate after the dose escalation part of the trial will be obtained on the basis of DLTs observed during the MTD evaluation period. However, for those patients who receive more than one cycle of the treatment, all AEs that constitute a DLT will be considered in the final determination of the dose recommended for the Phase II part.

As part of this additional analysis the probabilities of the Bayesian 2-parameter logistic regression model with overdose control will be also computed including all considered DLTs.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

No key secondary endpoints are defined in this study.

5.2.2 Secondary endpoints

The secondary endpoints in Phase I are

- RBC Transfusion Independence (RBC TI)
- Hematologic improvement neutrophils (HI-N)
- Hematologic improvement platelets (HI-P)
- Hematologic improvement erythroid (HI-E)
- Time to HI-E response
- Mean hemoglobin increase ≥ 1.5 g/dL
- Duration of Response (RBC Transfusion Independency, HI-N, HI-P, HI-E or Objective Response)
- Overall Objective Response (OR) [Complete Response (CR), Partial Response (PR), and Hematologic Improvement (HI)]

RBC Transfusion Independence (RBC-TI):

The definition of RBC TI is given in section 5.1.2.3 of the CTP. RBC-TI is evaluated in patients who are transfusion dependent at baseline. Percentages will be calculated using all treated patients, who are transfusion dependent at baseline, as the denominator.

The investigator's assessment as reported on the "Disease Assessment eCRF" will be used for the analysis of this endpoint. No derivation from the "Concomitant Blood Product Therapies eCRF" is planned. Consistency between these two eCRF pages will be reviewed during the trial's Medical Quality Review Meetings (MQRMs).

HI-N, HI-P and HI-E:

HI-N, HI-P and HI-E are defined in section 5.1.2.3 of the CTP. The investigator's assessment as reported on the "Disease Assessment eCRF" will be used for the analysis of these endpoints. No derivation from the "Laboratory eCRF" (or the "Concomitant Blood Product Therapies eCRF") is planned. Consistency between these eCRF pages will be reviewed during the trial's Medical Quality Review Meetings (MQRMs).

Time to HI-E response:

Time to HI-E response is defined only for patients who achieve a HI-E response as follows:

> Time to HI-E response [days] = date of first assessment indicating HI-E response – date of first administration of trial medication + 1.

Mean hemoglobin increase ≥ 1.5 g/dL:

The definition of "Mean hemoglobin increase ≥ 1.5 g/dL" is given in CTP section 5.1.2.3.

Duration of Response:

Duration of objective response is defined only for patients who achieve an overall response of CR or mCR or RBC TI.

Duration of response is defined as:

> Duration of Response [days] = date of outcome – date of first assessment indicating CR or mCR or RBC TI after first administration of trial medication + 1.

The censoring rules and dates of outcome (i.e. event or censoring) for Duration of Response under different scenarios are specified in Table 5.2.2:1. The evaluation period for duration of response is until treatment discontinuation (see also section 5.1.2.3 of the CTP).

Table 5.2.2:1 Derivation rules for Duration of Response

Situation	**Outcome (event or censored)**	**Date of outcome**
No relapse, no death	censored	Date of last disease assessment
Relapse (no subsequent anti-cancer therapy before relapse)	event	Date of disease assessment of relapse
Death without relapse, no subsequent anti-cancer therapy	censored	Date of death
Death without relapse, but subsequent anti-cancer therapy prior death	censored	Date of last disease assessment before initiation of subsequent anti-cancer therapy
Subsequent anti-cancer therapy before relapse (check interval between start of new medication and relapse)		
Interval <= 7 days	Event	Date of disease assessment of relapse
Interval > 7 days	Censored	Date of last disease assessment before initiation of subsequent anti-cancer therapy

Overall Objective Response:

Overall Objective Response is defined as Complete Response (CR), Partial Response (PR), HI-N, HI-P, or HI-E. A patient's " Overall Objective Response " = "Yes" if one of these responses was reported at least once throughout the trial.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

In the Phase I part, treatments are not randomized (open-label, dose escalation). Different dose levels (planned and intermediate) of the investigational medicinal product will be evaluated. The data will be presented for all dose cohorts separately, in particular, patients will be analysed by the treatment group initially assigned in the first treatment course. In addition, totals over all dose cohorts will be given.

"Analysing treatment periods" will be used for reporting of treatment emergent adverse events (AE) and to differentiate between screening, on-treatment, post-treatment and post-study safety data. The inequalities start date ≤ onset date of AE < stop date will determine whether the AE will be assigned to the "analysing treatment period" or not. Table 6.1:1 defines the "analysing treatment periods" which will be used for reporting of treatment emergent AEs and safety laboratory parameters.

Table 6.1:1 Definition of analysing treatment periods

Analysing treatment period	**Start date (including)**	**Stop date (excluding)**
Screening	Date of informed consent	Date of first administration of trial medication
MTD evaluation period	Date of first administration of trial medication	Date of third infusion or (if the third infusion was not administered) Date of first administration of trial medication + 28 days
On-treatment	Date of first administration of trial medication	Start date of 'Follow-up'
Follow-up	Date of end of REP +1 day, i.e. Date of last administration of trial medication + 30 days of REP + 1 day	Start date of 'Post-study'
Post-study	Last date patient status obtained / last date patient known to be alive + 1 (if patient is lost to follow-up) / date of refusal + 1 day / the date patient died + 1	DBL + 1 day

Data recorded between the first administration of trial medication until up to 30 days (Residual effect period; REP) after the last administration of trial medication will be considered as on-treatment.

In addition, to justify the MTD determination, AEs occurring during the MTD evaluation period will be presented separately from those occurring during the complete on-treatment period.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Even though no per protocol population is defined, patients with potentially important protocol deviations (iPD) will be identified and documented.

Potentially important protocol deviations are defined in Table 6.2:1. The final list of iPDs will be confirmed at the last report planning meeting (RPM) before the database lock at the time of the CTR.

If any manual iPDs are identified, they are to be summarized into categories and will be captured in the MQRM/RPM minutes via an accompanying Excel spreadsheet (3).

Table 6.2:1 Important protocol deviations

Category/ Code		Description	Comment/Example	Excluded from
A		**Inclusion/Exclusion Criteria**		
	A1	**Criteria related to safety**		
	A1.1[1]	Patient has condition that may cause additional risk from study medication	EX 11, IN 4	None
	A1.2[1]	Patient has laboratory assessments that may cause additional risk.	EX 6-9	None
	A1.3[1]	Patient is unable to comply with the protocol	EX 12, EX 21	None
	A1.4[1]	Patient has condition that may interfere with evaluation of safety (and/or efficacy)	EX 3-5, EX 10, EX 13, EX 17-20	None
	A2	**Criteria related to efficacy**		
	A2.1[1]	Patient does not have trial diagnosis or is not part of the target population	IN 1-3, EX 1, EX 2 (Phase II only)	None
B		**Legal criteria**		
	B1[1]	Informed consent not available/not done	IN 6	All
	B2[1]	Informed consent too late	Informed consent date after screening visit date.	None
	B3[1]	Men or women who are sexually active and not using adequate contraception.	EX 14, EX 15	None
	B4[1]	Pregnant or nursing female patient	EX 16, positive pregnancy test	None
	B5[1]	Patient's age < 18	IN 5	None
C		**Trial medication and randomization**		
	C1[2]	Administration of trial medication not in accordance with the protocol	As marked in the eCRF, after discussion and decision in MQRM	None
	C2[2]	Continuation of treatment although criteria for re-treatment are not met	Create listing, decision at MQRM / report planning meetings (RPM), see CTP section 4.1.4	None

Table 6.2:1 Important protocol deviations (cont.)

Category/ Code		Description	Comment/Example	Excluded from
	C3[2]	(Unjustified) intra-patient dose-escalation	Create listing, decision at MQRM / RPM, see CTP section 4.1.4	None
	C4[2]	Withdrawal of patient not performed according to CTP	Create listing, decision at MQRM / RPM, see CTP section 3.3.4	None
	C5[2]	Discontinuation of trial drug not performed according to CTP	Create listing, decision at MQRM / RPM, see CTP section 3.3.4	None
	C6[2]	Phase II: Wrong stratification factor input during randomization	Create listing comparing IVRS and eCRF information	None
D		**Restrictions**		
	D1[2]	Additional experimental anti-cancer, chemo-, immuno-, hormone - or radiotherapy during the treatment period.	Create listing, decision at MQRM / RPM, see CTP section 4.2.2.1 and EX 3, EX 5	None
E		**Missing data**		
	E1[2]	Baseline bone marrow assessment not within the required time-window	Create listing for patients whose bone marrow assessment was not within 14 days prior to first treatment, decision at MQRM / RPM	None

[1] iPD will be derived automatically
[2] iPD will be identified via individual review at MQRM/RPM/DBL

6.3 PATIENT SETS ANALYSED

The following patient sets are defined for the Phase I part:

- Screened set (SS): This patient set includes all patients who have signed the informed consent. The SS will be used for patient disposition tables.
- Treated set (TS): This patient set includes all patients who were documented to have received at least one dose of trial medication.
- MTD evaluation set: The MTD evaluation set includes all patients from the TS who have not been replaced for the MTD evaluation. Rules for replacement of patients are defined in Section 5.1 and CTP section 3.3.4.1.

The MTD evaluation set will be used for the primary endpoint analyses whereas the TS will be used for all other efficacy and safety analyses in the Phase I part. The list of replaced patients will be provided by the clinical trial monitor no later than at the last RPM and will be attached to the RPM minutes.

No per protocol population will be used for analyses.

6.5 POOLING OF CENTERS

Not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

If not stated otherwise, missing data will not be imputed and will remain missing. Potential outliers will be reported and analysed as observed. Missing or incomplete AE dates will be imputed according to BI standards (4).

For missing laboratory data at Visit 1 (before the very first administration of study medication) data from preceding visits will be used if available.

6.7 BASELINE, TIME WINDOWS, AND CALCULATED VISITS

Study days and visits will be labelled according to the CTP's flow chart.

Unless otherwise specified, baseline is defined as the time-point closest to but prior to the first administration of trial medication in course 1. Note that for some trial procedures (for example body weight, vital signs, laboratory tests) this may be the value measured on the same day the trial medication was started. In these cases it will be assumed that the measurements were taken according to protocol, i.e. prior to first intake of any trial medication.

For laboratory values, baseline is defined as the latest time-point before the very first administration of any trial medication in course 1. When not only the examination date but also time are recorded, the examination time has to be taken into account when defining baseline. That is, a laboratory value on the same date as the first trial drug administration is considered as baseline value if and only if the time of laboratory value is before or the same as the time of first trial drug administration.

7. PLANNED ANALYSES

The labelling and display format of statistical parameters will follow the guideline "Standards for Reporting of Clinical Trials and Project Summaries" (5).

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard deviation (SD) / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles will be preferred to mean, standard deviation, minimum and maximum.

In general, means, SDs, medians, and percentiles will be presented to one more decimal place than the raw data. Minima and maxima will be presented to the same number of decimal places as the raw data.

Duration and time-to-event data will be listed only. If not specified otherwise, durations and time-to-events will be displayed in months and a final decision will be made at the last RPM.

Tabulations of frequencies for categorical data will include all possible categories, even when the count is zero. The display will include the number of observations in a category as well as the percentage (%) relative to the number of patients in the respective treatment group. The percentages will be calculated out of all patients in the corresponding patient sets regardless of whether they have non-missing values or not, unless otherwise specified. Percentages will be rounded to one decimal place. The category "missing" will be displayed if and only if there are actually missing values.

If a table presents only categorical data, "N (%)" will be displayed in the column header only.

Abbreviations (e.g., Wors.) or acronyms (e.g., PD) will not be displayed in tables and Subject Data Listings (SDLs) without any explanation. They will be either spelled out or explained in footnotes.

If applicable, conversion from days to weeks, months and years will be as follows:

- Weeks = days ÷ 7
- Months = 12 × days ÷ 365.25
- Years = days ÷ 365.25

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Standard descriptive analyses and summary tables are planned for this section of the report. Data will be summarized by treatment group. A "total" column will also be included in the summary tables.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.

Concomitant diseases will be coded similarly as for adverse events based on the most current version of Medical Dictionary for Regulatory Activities (MedDRA). Concomitant therapies (CTs) will be coded according to World Health Organization Drug Dictionary (WHO DD). CTs will be categorized by therapy type according to the third level of the Anatomical,

Therapeutic, Chemical (ATC) classification system. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level 3 category will be counted more than once; footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

A listing of medication compliance will be provided in the corresponding section of the report.

7.4 PRIMARY ENDPOINTS

The primary endpoints are the MTD and the number of patients with dose limiting toxicities (DLTs) during the MTD evaluation period. The MTD is determined from the number of non-replaced patients with DLT during the MTD evaluation period (for the definition of MTD evaluation period refer to Section 5.1).

An overall summary of patients with DLT(s) which occurred during the MTD evaluation period and the on-treatment period will be provided for each dose cohort.

Patients who were treated but replaced will be not considered for the MTD determination. However, all information, including adverse events qualifying for a DLT from later times, will be considered in the final determination of the recommended Phase II dose (RP2D).

The analysis of the MTD is based on a Bayesian logistic regression model (BLRM). The MTD is defined as the highest dose for a given schedule that is expected to cause less than 25% risk of the true DLT rate being above or equal to 33% during the MTD evaluation period. Estimation of the MTD during the dose escalation phase of the study will be based upon the estimation of the posterior probability of the incidence of DLT in toxicity categories during the MTD evaluation period for all evaluable patients. The model to be used is specified in CTP section 7.

Tables and bar charts will be produced to display, for each dose level, the posterior probabilities that the true DLT rate being in the underdosing [0, 0.16), target-dosing [0.16, 0.33) and overdosing [0.33, 1] intervals.

In order to describe the occurred dose escalation steps, a listing of all treated patients will be provided. This will include the initial dose of BI 836858, patient number, treatment start date, DLT in MTD evaluation period [y/n], evaluable for MTD [y/n]. The listing will be sorted by treatment start date.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Other secondary endpoints

The analysis of secondary endpoints in Phase I will be performed in a descriptive manner. No inferential analysis will be conducted. The secondary endpoints RBC-TI, HI-N,HI-P, HI-E, mean hemoglobin increase ≥ 1.5 g/dL and overall objective response will be summarized in a frequency table. Hereby the data will be presented for all dose cohorts separately as well as in total. Time-to-HI-E responses and durations of response will be listed only.

7.7 EXTENT OF EXPOSURE

Standard descriptive analyses over all treatment courses will be performed. This will include a summary of the variables defined in Section 5.4.2 and will comprise a mixture of frequency and percentages, as well as summary statistics.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set, except for analyses pertaining to MTD determination described in Section 7.4 which will then be performed on the MTD evaluation set. Patients who were replaced within the MTD evaluation period will be excluded from the determination of the MTD but will be considered for all other safety evaluations. A listing of replaced patients will be provided.

7.8.1 Adverse events

7.8.1.1 Maximum tolerated dose and dose limiting toxicity

Analysis of MTD will be reported as described in Section 7.4.

In addition, tables displaying DLTs by primary system organ class and preferred term will be provided by initial treatment for the MTD evaluation period for the MTD evaluation set as well as for the treated set over the on-treatment period.

The purpose of these tables is to summarize and document the data that led to the selection of MTD. A summary of the number of patients with DLT within the MTD evaluation period (treatment course 1) and for all treatment courses of the on-treatment period will be given by initial treatment for the treated set.

7.8.1.2 Adverse events

Unless otherwise specified, the analyses of adverse events (AEs) will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT the number of AEs. The analyses will be based on BI standards. Adverse events will be coded with the most recent version of MedDRA. The severity of AEs will be scaled according to CTCAE version 4.0.

For analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences.
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence.

For each patient, all episodes with the same preferred term (PT) (system organ class, SOC) will be condensed to one AE record using a worst case approach for all AE attributes including CTCAE grading.

The analysis of adverse events will be based on the concept of treatment emergent adverse events, where a treatment emergent AE has an onset in the analyzing treatment period. All adverse events occurring before first intake of trial medication will be assigned to 'screening' and all adverse events occurring after last intake of trial medication + 30 days will be assigned to 'post-treatment' (in randomized trials for listings only). For details on the treatment definition, see Section 6.1. In addition, a listing will be provided, detailing the actual treatment on the day when the adverse event started. For screening and post-study period, AEs will be listed.

An overall summary of adverse events will be presented. This will include the number of patients with AEs by the highest CTCAE grade. The frequency of patients with adverse events will be summarized by treatment, highest CTCAE grade, primary system organ class and preferred term (PT). Separate tables will be provided for the followings:

- serious adverse events (SAEs),
- drug-related SAEs,
- drug-related AEs,
- AEs leading to permanent discontinuation of trial medication,
- AEs leading to death,
- DLTs, and
- adverse events of special interest (AESIs) including infusion related reactions (IRRs).

In addition, tables will be provided for patients with AEs of incidence ≥ 10% and with drug-related AEs of incidence ≥ 10%.

Tabulations of AEs using user-defined AE categories will also be provided.

Adverse events of special interest (AESIs):

Adverse events of special interest (AESIs) are defined in CTP section 5.2.2.1 as infusion related reactions (IRRs) of CTCAE grade >= 3, DLTs (occurring during the MTD evaluation period or repeated treatment courses) and drug induced liver injury (DILI).

Other significant AEs:

Other significant AEs are defined as serious and non-serious AEs that lead to dose reduction or permanent discontinuation of study medication. Their incidence will be reported by severity according to CTCAE grades.

Infusion related reactions (IRRs):

IRRs will be the object of special attention.

Patients with any IRR will be tabulated by treatment and worst CTCAE grade. In addition, the number of infusions and the number of IRRs will be displayed by treatment.

The duration of IRR [h] and the time since start of the respective infusion [min] together with IRR related symptoms will be tabulated by infusion number and overall.

- Duration of IRR [h] = (End time of IRR - Start time of IRR) [seconds] / 3600
- Time since start of the respective infusion [min] = (Start time of IRR - Start time of infusion) [seconds] / 60

The relationship between the occurrence of IRRs and infusion rate as well as the administration of premedication will be examined.

Duration of IRR, time since start of infusion, and related symptoms will be summarized descriptively by infusion timepoints.

Fatal AEs:

AEs leading to death during the on-treatment period will be tabulated. Reported fatal AEs that occurred in the post-treatment phase will be listed.

Additionally, a table summarizing the information on deaths collected on the AE eCRF and the Patient Status eCRF will be provided.

User defined AE categories (UDAEC):

User defined AE categories (UDAEC) are defined in Table 7.8.1.2:1. For UDAECs which contain sub-searches and/or two sensitivity levels (broad and narrow) all possibilities will be displayed on the UDAEC level in tables. For example for UDAEC “Bleeding”, it will include “Bleeding - SMQ Haemorrhage”, “Bleeding - SMQ Haemorrhage laboratory terms broad”, “Bleeding - SMQ Haemorrhage laboratory terms narrow” and “Bleeding - SMQ Haemorrhage terms (excl. laboratory terms) narrow”.

Table 7.8.1.2:1 Definition of user defined AE categories

Special Search Category	**Definition**	**Sensitivity**
Infusion related reactions (hypersensitivity)	SMQ 20000021 + infusion related reaction PT 10051792	Narrow (Algorithm)
Bleeding	SMQ Haemorrhage 20000038	Narrow & broad
	SMQ Haemorrhage terms (excl. laboratory terms) 20000039	Narrow
	SMQ Haemorrhage laboratory terms 20000040	Narrow & broad
Nausea	BIcMQ Nausea 30000078	Narrow & broad
Vomiting	BIcMQ Vomiting 30000091	Narrow & broad
Drug related hepatic disorders	SMQ Drug related hepatic disorders 20000006	Narrow & broad
	SMQ Cholestasis and jaundice of hepatic origin 20000009	Narrow & broad
	SMQ Drug related hepatic disorders - severe events only 20000007	Narrow & broad
	SMQ Liver related investigations, signs and symptoms 20000008	Narrow & broad
	SMQ Liver-related coagulation and bleeding disturbances 20000015	Narrow & broad
ALT	BIcMQ Elevated Specific Liver Function Parameters sub-search1 30000022	Narrow & broad
AST	BIcMQ Elevated Specific Liver Function Parameters sub-search2 30000023	Narrow & broad
ALKP	BIcMQ Elevated Specific Liver Function Parameters sub-search3 30000024	Narrow & broad
gGT	BIcMQ Elevated Specific Liver Function Parameters sub-search4 30000025	Narrow & broad
Bilirubin	BIcMQ Elevated Specific Liver Function Parameters sub-search5 30000026	Narrow & broad
Neutropenia	BIcMQ Neutropenia 30000031	Narrow & broad
Cardiac disorders[1]	SMQ Ischaemic heart disease 20000043	Narrow & broad
	SMQ Cardiac failure 20000004	Narrow & broad
	SMQ Cardiac arrhythmias 20000049	Narrow & broad

Table 7.8.1.2:1 Definition of user defined AE categories (cont.)

Special Search Category	Definition	Sensitivity
Tumour Lysis Syndrome	SMQ Tumour Lysis Syndrome 20000219	All broad
	SMQ Torsade de point/QT prolongation Broad (20000001)	
	SMQ Cardiac arrhythmia terms broad (incl bradyarrhythmias and tachyarrhythmias) (20000050)	
	SMQ Convulsions broad (20000079)	
Fluid accumulation	HLT Total fluid volume increased 10044085	
	HLT Oedema NEC 10030113	
	HLT Pulmonary oedemas 10037424	
	HLT Pneumothorax and pleural effusions NEC 10035761	
	PT Ascites 10003445	
	PT Abnormal weight gain 10000188	
Infections	Infections (incl. respiratory infections and sepsis) - SOC 10021881 use label "Infections and infestations"	
	Infections (incl. respiratory infections and sepsis) - HLGT 10024970 use label "Respiratory tract infections"	
	Infections (incl. respiratory infections and sepsis) - HLT 10040054 use label "Sepsis, bacteraemia, viraemia and fungaemia NEC"	
Inflamed gut	PT Enterocolitis 10014893	
	PT Enterocolitis bacterial 10065206	
	PT Enterocolitis fungal 10065205	
	PT Enterocolitis helminthic 10065204	
	PT Enterocolitis infectious 10058838	
	PT Enterocolitis viral 10061841	
	PT Colitis 10009887	
	PT Enteritis 10014866	
Acute febrile neutrophilic dermatosis	PT Acute febrile neutrophilic dermatosis 10000748	

[1] A BIcMQ has been requested, however, as long as this is not available the terns as defined in Table 7.8.1.2:2 will be used.

Table 7.8.1.2:2 User defined (sub-) search category of "Cardiac Failure"

Selected PTs for Cardiac Failure
Cardiac asthma
Cardiac failure
Cardiac failure acute
Cardiac failure chronic
Cardiac failure congestive
Cardiac failure high output
Cardiac index decreased
Cardiac output decreased
Cardiogenic shock
Cardiomegaly
Cardiothoracic ratio increased
Dilatation ventricular
Left ventricular failure
Low cardiac output syndrome
Right ventricular failure
Oedema due to cardiac disease
Left ventricular dysfunction
Ejection fraction decreased
Cardiopulmonary failure
Diastolic dysfunction
Cardiac ventriculogram right abnormal
Cardiac ventriculogram abnormal
Cardiac ventriculogram left abnormal
Cardiac cirrhosis
Right ventricular dysfunction
Ventricular dysfunction
Cardiac resynchronisation therapy
Ventricular failure
Acute left ventricular failure
Acute right ventricular failure
Chronic left ventricular failure
Chronic right ventricular failure
Myocardial depression
Ventricular dyssynchrony
Systolic dysfunction
Neonatal cardiac failure

UDAEC will be summarized by dose cohort, search category, preferred term and CTCAE grade. Some events contribute to more than one UDAEC. Patients with such AEs are counted in each of the UDAEC but are counted only once in the overall number of patients with an AE in any UDAEC.

Tumor Lysis Syndrome

In patients with a high tumor burden who are exposed to a highly effective therapy, there is a risk of rapid tumor destruction resulting in Tumor Lysis Syndrome (TLS). Patients will be identified as having potential TLS if they meet both of the following criteria:

(1) Two or more of the laboratory parameters meet the criteria in Table 7.8.1.2:3.
    a. Time window
        i. on the day of BI 836858 infusion or the following 6 days,
        ii. at least two of the qualifying lab values must have occurred within the same 24 hour period
(2) Have an adverse event identified by any of the SMQ in table 7.8.1.2:4 or have a qualifying creatinine value.
    a. Time window
        i. AE onset or creatinine observation at any time during the treatment or residual effect period

Laboratory tests relevant to TLS and patients with potential TLS will be displayed in listings.

Table 7.8.1.2:3 Laboratory Signs of Cell Destruction

Laboratory parameter	**Abnormal value**
Uric acid	≥476 µmol/L AND increase from relative baseline[1] by ≥25%
Potassium	value ≥ 6.0 mmol/L AND relative baseline < 6.0 mmol/L
Inorganic phosphate	≥1.45 mmol/L AND increase from relative baseline by ≥25%
Calcium	<7 mg/dL[2] AND decrease from relative baseline by ≥25%

[1]Relative baseline is derived separately for each BI 836858 infusion as the last value prior to that BI 836858 infusion. Relative baseline will be derived independently for the four parameters, ie. four baseline values do not necessarily have to be derived from the same laboratory assessment. [2]For calcium, 0.25* mg/dL= mmol/L

Table 7.8.1.2:4 Clinical Signs of Cell Destruction

Criterion
TLS broad SMQ [20000219]
Torsade de point/QT prolongation broad SMQ [20000001]
Cardiac arrhythmia terms broad SMQ (incl bradyarrhythmias and tachyarrhythmias) [20000050]
Convulsions broad SMQ [20000079]
Creatinine Absolute increase from relative baseline by 26.5 µmol/L AND increase from relative baseline by ≥50%

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8). The same on-treatment period as considered for the analysis of AEs will be applied for laboratory values. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses.

Safety laboratory examinations include hematology, biochemistry, coagulation and qualitative urine analysis:

Hematology	Hemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential (neutrophils, basophils lymphocytes, monocytes, eosinophil, reticulocytes), platelets (PLT)
Biochemistry	Glucose (plasma), sodium, potassium, calcium, inorganic phosphate, creatinine, AST, ALT, alkaline phosphatase (AP), lactate dehydrogenase (LDH), bilirubin (total and direct), urea (preferred) or BUN, total protein, albumin, uric acid, IgG, IgM, IgA and direct antiglobulin (direct Coombs), Free haemoglobin(serum), Haptoglobin
Coagulation	Activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalised ratio (INR) where indicated (e.g. treatment with vitamin K antagonists)
Urine	pH, glucose, erythrocytes, leukocytes, protein, nitrite

Neutrophil and platelet counts of each patients will be plotted in log scale graphs.

Descriptive statistics, including change from baseline and frequency of patients with transitions relative to the reference range, will be provided. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE version 4.0. The following outputs will be presented:

- Worst CTCAE grade experienced during the on-treatment phase.
- Transitions of CTCAE grade from baseline to worst laboratory value, from worst to last laboratory value during the on-treatment phase, and from baseline to last laboratory value.

Worse laboratory value and its CTCAE grade (highest CTCAE grade) over all courses will be calculated for each laboratory parameter.

The last laboratory value on treatment is the laboratory value of the last visit during the on treatment period of each patient.

Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline values will be displayed in the category “Missing CTCAE grade at baseline” for those laboratory parameters where CTCAE grading is applicable.

Possible clinically significant abnormal laboratory values:

Possible clinically significant abnormal laboratory values are defined as those laboratory values that are of CTCAE Grade ≥ 2 and show an increase from baseline value by at least one CTCAE grade. For those parameters for which no CTCAE has been defined, BI standard definition will be used to determine possible clinical significance. Frequency of patients with

possible clinically significant abnormal laboratory values will be provided whenever applicable. If no baseline value is available but the patient has a post-baseline laboratory value of CTCAE Grade ≥ 2 an increase from baseline will be assumed, i.e. the laboratory value considered as possible clinically significant.

Handling of laboratory parameters with CTCAE grade -1 and -9:

For calculating the change in CTCAE grade from baseline, patients with a CTCAE grade of -9 (no CTCAE grade defined) will be treated as a CTCAE grade 0 for all analyses. In laboratory listings, the CTCAE grade will be displayed as -9.

For Uric Acid, Glomerular filtration rate (GFR) and Hypokalemia, the CTCAE grade cannot always be assigned by the laboratory parameter itself as two different CTCAE grades have the same laboratory constellation, but are distinguished by additional clinical parameter. In this case a CTCAE grade of "-1" will be assigned initially. For all analyses, patients with a CTCAE grade of "-1" will be treated as

- Grade 1 for Uric Acid,
- Grade 3 for GFR, and
- Grade 1 for Hypokalemia.

In laboratory data listings, the CTCAE grade will be displayed as -1.

Handling of Urine protein (UPROZ)

For urine measurement based on dipsticks the indicated results will be converted as follows for the analysis:

Table 7.8.2:1 Conversion of urine measurements based on dipsticks

Original dipstick measurement	Converted dipstick measurement
“-” ; “NEG” ; “NEGATIVE” ; “NORMAL”	0.0
“0.5” ; “TRACES” ; “TRACE” ; “+/-” ; “+-” ; “-/+”	0.5
“+” ; “1+”	1.0
“++” ; “2+”	2.0
“+++” ; “3+”	3.0
“++++” ; “4+”	4.0

In CTCAE Version 4.0 a 24 hours urine sample should be performed if the dipstick measurement is at least “2+” and the CTCAE grade should then be determined based on the 24 hours urine sample. Urine protein 1.0 – 3.4 g/24hrs is graded as CTCAE grade 2 and urine protein ≥ 3.5 g/24hrs is graded as CTCAE grade 3. As this definition aggregates different urine analysis measurements, this will not be considered for laboratory analyses, but should be considered by the investigator when grading adverse events.

To ensure medically rational and consistent (within BI) handling of urine protein assessed by dipstick only, no analyses based on CTCAE grades will be done. Instead urine protein will be

converted as for other urine measurements based on dipsticks (outlined in Table 7.8.2:1) and displayed in the urine analysis tables.

Hepatic injury:

As defined in the CTP a hepatic injury (DILI) is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT >3 fold ULN combined with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

Potential Hepatic enzyme elevations (potential Hy's law cases):

In addition, the following definition of potential Hy's law cases was discussed with the FDA at the pre-NDA meeting of the NSCLC submissions of the nintedanib trials 1199.13 and 1199.14 and was agreed by the authorities. Please also refer to the FDA guideline Guidance for Industry Drug- Induced Liver Injury: Premarketing Clinical Evaluation, version of July 2009.

These are defined as those cases where a combination of all of the following events occurred: any on-treatment value of ALT or AST (or both) > 3 times upper limit of normal (3 x ULN) with total bilirubin ≥ 2 x ULN and ALKP < 2 x ULN. The events can occur in any order, but must occur within 14 days of the previous event, i.e. the second event must occur within 14 days of the first event, and the third event must occur within 14 days of the second event, etc. Figure 7.8.2:1 gives 2 examples, first where the criterion is satisfied and second where it is not satisfied.

All of the above combinations of elevated liver enzymes will be analysed, i.e. DILI cases as defined in the CTP and additionally the definition of potential Hy's law cases which was discussed with the FDA by the nintedanib project. A listing with detail hepatic enzymes values will be created for the subjects who satisfied the condition. eDISH plot for ALT and total bilirubin will be displayed.

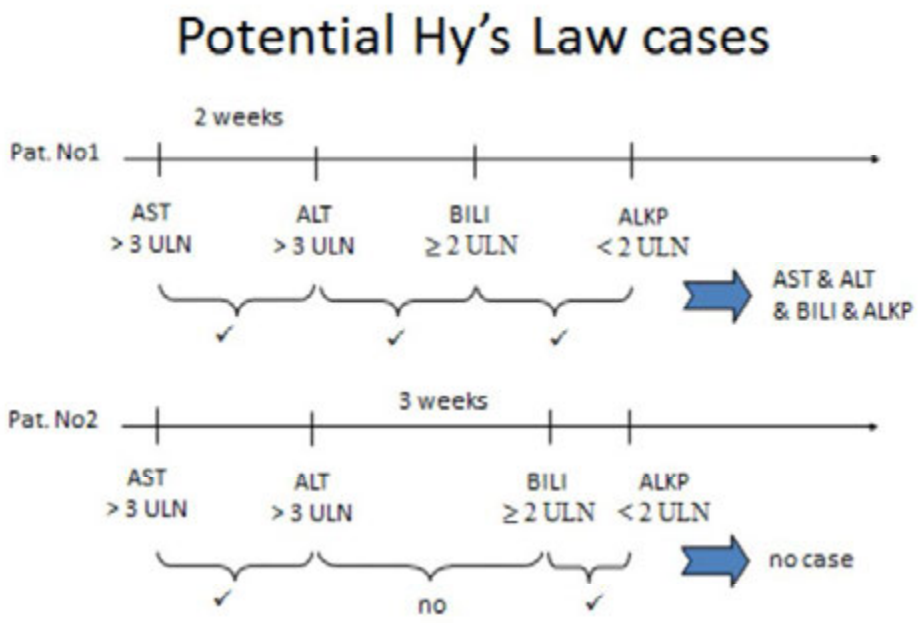

Figure 7.8.2:1 Assessment of patients fulfilling the criteria for potential Hy's law cases. Top: patient fulfils criteria. Bottom: patient does not fulfil criteria.

7.8.3 Vital signs

Only descriptive statistics are planned for the analysis of vital signs. Observed values and changes from baseline will be summarized.

7.8.4 ECG

12-lead resting ECGs are done throughout the trial and are assessed for clinically relevant results which are to be recorded as either concomitant disease or AE by the investigator. No further ECG analysis is planned.

7.8.5 Others

Pregnancy tests:
A listing showing the results of pregnancy tests will be provided.

8. REFERENCES

1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	*001-MCS-50-415_RD-01*: "TSAP annotations", current version, IDEA for CON.
3	*001-MCS-40-413*: "Identify and Manage Important Protocol Deviations (iPD)", current version, IDEA for CON.
4	*BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version; IDEA for CON.
5	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
6	*001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
7	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
8	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

10. HISTORY TABLE

Table 10:1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Initial	**20-Dec-16**		None	This is a draft TSAP.
Final	**07-JAN-2020**		All	This is the final TSAP. This study has been terminated prematurely and no patient has been recruited for the Phase II part. Section 4 clarifies that no planned analysis for Phase 2 in the CTP will be conduct. Sections 5 to 7 are updated with Phase II related content removed and minor edits. Section 8 is updated to the latest BI internal reference document.